

U.S.S.N. 09/067,337

KÖSTER et al.

AMENDMENT AND RESPONSE

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Conclu

alkylarylamino, alkylcarbonylamino, alkoxycarbonylamino, arylcarbonylamino, aryloxycarbonylamino, azido, alkylthio, arylthio, perfluoroalkylthio, thiocyno, isothiocyno, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl or diarylaminosulfonyl; R²⁰ is alkylene, alkenylene, alkynylene, arylene or heteroarylene; k is 2 or 3; and j is 0 or 1.

REMARKS

Any fees that may be due in connection with filing this paper, or with this application or the parent application during their entire pendency, may be charged to Deposit Account No. 50-1213. If a Petition for Extension of Time is required, this paper is to be considered such petition.

Claims 5-7, 11-16, 29, 33-37, 39, 45 and 49 are pending herein. Claims 8, 9, 10, 17-28, 30-32, 38, 40-44 and 46-48 are cancelled herein without prejudice or disclaimer solely in the interest of advancing the prosecution of this application to allowance. Applicant reserves the right to file divisional applications directed to any cancelled subject matter.

Claims 5, 7, 11-14, 33, 37, 39 and 45 are amended herein. Basis for the amendments to the claims may be found in the claims as originally filed and in the specification. In particular, amendment to claim 5 finds basis in original claim 5 and in the specification as originally filed, on page 4, lines 5-8. Amendment to claim 33 finds basis in original claims 33 and 38.

ELECTION OF SPECIES

The Office Action acknowledges the Election of Species filed on August 6, 2001, drawn to liquid phase carriers which do not contain 2'-deoxythymidine-3'-O-yl and further states that claims 5-9, 27-40 and 45-49 are being examined in the instant Office Action.

Applicant respectfully submits that species represented by formula Ia, were elected on January 18, 2000, in a Response to Requirement for Election mailed on October 4, 1999. Applicant further elected species drawn to liquid

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phase carriers which do not contain 2'-deoxythymidine-3'-O-yl, on August 6, 2001, in a Response to Requirement for Election mailed on October 4, 1999. Currently pending claims ~~5-7, 9-16, 29, 33-38 and 49~~, following entry of the above amendment, read on the elected species drawn to liquid phase carriers of formula Ia, which do not contain 2'-deoxythymidine-3'-O-yl.

PROVISIONAL REJECTION OF CLAIMS 5-9, 27-40, AND 45-49 FOR OBVIOUSNESS-TYPE DOUBLE PATENTING

Claims 5-9, 27-40 and 45-49 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting over the claims of copending U.S. application Serial No. 09/484,484. It is alleged in the Office Action that the claims in both the application are drawn to a liquid phase carrier (LPC), all being drawn from the same structural formulae and the substantial overlap in structure and intended modifications to the core of the structures represent subject matter covered by both applications claims.

Since obviousness-type double patenting cannot be assessed until there is allowable subject matter, applicant respectfully requests deferral of this issue until an indication that there is allowable subject matter in one of the cases. Until that time, the propriety of the rejection cannot be properly assessed. If, upon review of the claims pending at the time, the need for a Terminal Disclaimer will be assessed, and, if needed, a Terminal Disclaimer will be provided.

REJECTION OF CLAIMS 5-9, 27-40 and 45-49 UNDER 35 U.S.C. §103(a)

Claims 5-9, 27-40 and 45-49 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over the teachings of U.S. Patent No. 5,198,540, to Köster et al. The Office Action alleges that the compounds of Köster et al. include LPCs possessing two to four points of attachment, which overlap with applicants optional number of points of attachment which include 3 to 6 points of attachment. The Office Action further alleges that the process claims of Köster et. al/ patent render applicants claimed methods *prima facie* obvious. It

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is alleged in the Office Action that the use of a known member of a class of materials (LPCs in the instant case) in a process to produce the expected product (oligonucleotide) or result (biopolymeric synthesis) is not patentable if other members of the same class are known to be useful for the same purpose, even though the results are better than expected.

The Office Action notes that there are some differences between the compounds claimed and those of the prior art, specifically the instantly claimed LPCs have additional points of attachment. The Office Action concludes that the cited reference renders the instantly claimed LPCs *prima facie* obvious. Applicant respectfully traverses this rejection.

Relevant Law

[I]n order to establish a *prima facie* case of obviousness, there must be evidence, preferably a teaching, suggestion, incentive or inference from the cited art or in the form of generally available knowledge that one of ordinary skill would have been led to modify the relevant teaching to arrive at what is claimed. *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963).

The prior art must provide a motivation whereby one of ordinary skill in the art would have been led to do that which the applicant has done. *Stratoflex Inc. v Aeroquip Corp.*, 713 F.2d 1530, 1535, 218 USPQ 871, 876 (Fed. Cir. 1983). In addition, the mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification. *In re Fritch*, 23 USPQ 1783 (Fed. Cir. 1992).

In addition, unexpected properties must always be considered in the determination of obviousness. A compound's structure and properties are inseparable so that unexpected properties are part of the subject matter as a whole. *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963).

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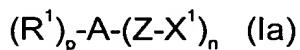
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The instant claims

Applicant respectfully brings it to Examiner's attention that claim 1 was cancelled in an amendment filed on March 12, 2001.

Instant claim 5 is directed to a liquid phase carrier (LPC) of formula (la):



where:

A is silicon;

n is 3 or 4; and

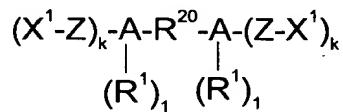
the remaining variables are as defined therein.

Claims 6, 7 and 9-16 further define the variables in claim 5.

Claim 29 is directed to the LPC of claim 5 coupled to a photocleavable linker.

Claim 33 is directed to a method of solution phase biopolymer synthesis using an LPC of formula $(R^1)_p-A-(Z_t-X^1)_n$, wherein the variables are as defined therein. Claims 34-37 and 39 further define the method of claim 33.

Claim 45 is directed to an LPC of formulae:



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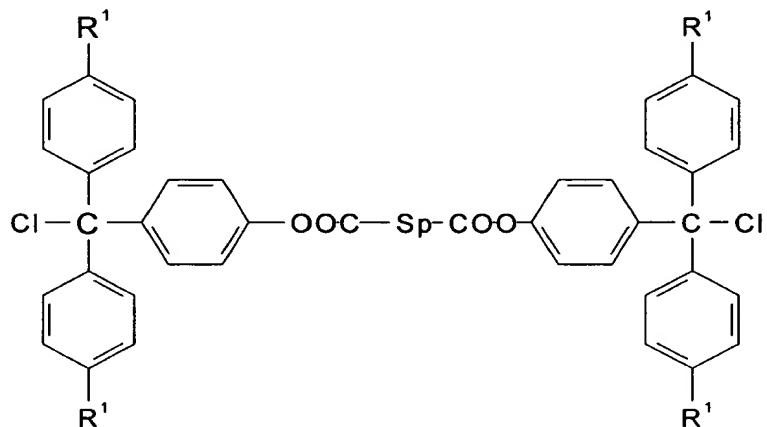
AMENDMENT AND RESPONSE

where the variables are as defined therein.

Claim 49 is directed to the LPC of claim 5 coupled to a biopolymer.

Differences between the teachings of Köster *et al.* and the instant claims

U.S. Patent No. 5,198,540, to Köster *et al.*, teaches LPCs possessing two to four points of attachment of formula Sp(X)_n, where X is a reactive group which is compatible from the point of view of nucleotide chemistry, n is an integer from 2 to 4, and Sp is an optionally branched alkylene or polyalkylene group, an arylene or polyarylene group, a polyaralkylene group, a polyester, a polyamide, a polysiloxane, an optionally branched alkylenedioxy compound or optionally partially alkylated polyalkyleneoxy compound. The cited reference also teaches LPCs possessing two points of attachment having formulae:



In instant claims 5-7, 9-16, 29, 33-37, 39, 45 and 49, the LPCs have formula Ia, where A is silicon, and there are 3, 4 or 6 points of attachments.

The LPCs of claim 5

Applicant respectfully submits that the cited reference does not teach or suggest the LPCs of instant claim 5 with formula Ia (LPCs with 3 to 4 points of

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attachments) wherein A is silicon. Neither does it teach or suggest the structural modifications required to modify the LPCs taught therein to arrive at the LPCs of instant formula Ia having a center of symmetry at a silicon atom.

Thus, one of ordinary skill in the art, given the teachings of Köster *et al.*, would not have motivated to do what applicant has done. Absent such motivation, the LPCs of instant claim 5 are not *prima facie* obvious over Köster *et al.*.

The LPCs of claim 45

The LPCs of instant claim 45 possess 4 or 6 points of attachment and are composed of two of the groups of formula (Ia), where A is silicon, linked together by R²⁰, wherein R²⁰ is alkylene, alkenylene, alkynylene, arylene or heteroarylene. The cited art does not teach or suggest such LPCs. Neither does it teach or suggest the structural modifications to the LPCs taught therein to arrive at the LPCs of instant claim 45.

Thus, one of ordinary skill in the art, given the teachings of Köster *et al.*, would not have motivated to do what applicant has done. Absent such motivation, the LPCs of instant claim 45 are not *prima facie* obvious over Köster *et al.*.

Methods of using LPCs

Furthermore, the cited reference does not teach or suggest methods of using LPCs of instant formula Ia, where A is silicon, in solution phase biopolymer synthesis, as claimed in instant claims 33-37 and 39, because as discussed above, it does not teach or suggest the LPCs of instant formula Ia. Neither does it teach or suggest the structural modifications required to modify the LPCs disclosed therein to arrive at the instant LPCs, having a center of symmetry at a silicon atom for use in the instant methods.

Absent such teaching or suggestion, one of ordinary skill in the art would not have been motivated to do what applicant has done. Applicant respectfully submits that one of ordinary skill in the art, given the teachings of U.S. Patent

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No. 5,198,540, would not have been motivated to prepare the LPCs of instant formula Ia, for use in solution phase biopolymer synthesis. Absent such motivation, the instant claims are not *prima facie* obvious over the teachings of the cited reference.

Therefore, the Office Action fails to establish a *prima facie* case of obviousness for the LPCs of the instant claims.

In order to establish a *prima facie* case of obviousness, there must be some teaching or suggestion in the cited art that would motivate one of ordinary skill in the art to do what applicant has done. It is respectfully submitted that no such motivation exists in U.S. Patent No. 5,198,540. The cited reference teaches a generic class of LPCs possessing 2 to 4 points of attachment. The cited reference neither teaches or suggests the instantly claimed LPCs of formula Ia, where A is silicon, and of instant claim 45, possessing 4 or 6 points of attachment. Nor does it teach or suggest the structural modifications required to modify the LPCs taught therein to arrive at these LPCs.

Since the cited reference does not teach or suggest LPCs of the instant claim 5, it cannot teach or suggest methods of solution phase biopolymer synthesis using the LPCs of the instant claim, nor can it teach or suggest the LPCs of the instant claim, coupled to a biopolymer. Therefore, the Office Action has failed to set forth a *prima facie* case of obviousness for these LPCs of the instant claims.

Rebuttal to the specific arguments in the Office Action

1. It is alleged in the Office Action that the compounds of Köster *et al.* include LPCs possessing 2 to 4 points of attachments, which overlaps with applicant's optional number of points of attachment which include 3 to 6 points of attachment and that the overlap is undeniable.

The applicant respectfully submits that as discussed above, the instantly claimed LPCs are structurally different than the LPCs in Köster *et al.* reference, therefore there is no overlap between these formulae and the teachings of

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Köster *et al.* The instantly claimed LPCs and the methods of biopolymer synthesis using the LPCs, are not taught or suggested in the cited reference.

2. The Office Action alleges that it would have been obvious to one having ordinary skill in the art at the time of the invention was made to formulate LPCs with multiple points of attachment and variable structure, because the prior art teaches such LPCs.

The applicant respectfully submits that as discussed above, the prior art **does not** teach or suggest the LPCs of instant claims. Neither does it teach or suggest the structural modifications required to modify the LPCs taught therein needed to arrive at the LPCs of the instant claims. Therefore, the cited reference does not provide any motivation to prepare the LPCs of instant formula Ia. Absent such a motivation, LPCs of claims are not *prima facia* obvious over the teachings of the cited art.

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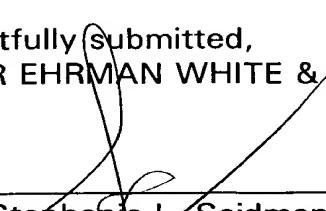
Applicant respectfully requests reconsideration and withdrawal of this rejection.

* * *

In view of the above, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,
HELLER EHRLMAN WHITE & McAULIFFE LLP

By:


Stephanie L. Seidman
Registration No. 33,779

Attorney Docket No. 24743-2301

Address all correspondence to:

Stephanie L. Seidman, Esq.

HELLER EHRLMAN WHITE & McAULIFFE LLP

4350 La Jolla Village Drive, 7th Floor

San Diego, California 92122

Telephone: (858) 450-8400

Facsimile: (858) 587-5360

EMAIL: sseidman@hewm.com

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: KÖSTER *et al.*
Serial No.: 09/067,337
Confirmation No.: 9981
Filed: April 27, 1998
For: **SOLUTION PHASE BIOPOLYMER
SYNTHESIS**
Art Unit: 1623
Examiner: Wilson, J.

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ATTACHMENTS TO RESPONSE TO OFFICE ACTION

The following attachment is provided:

- (1) Marked up claims 5, 7, 11-14, 33, 37, 39 and 45 in accord with
37 CFR §1.121.

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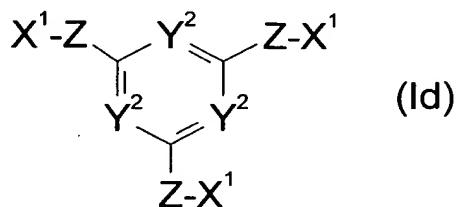
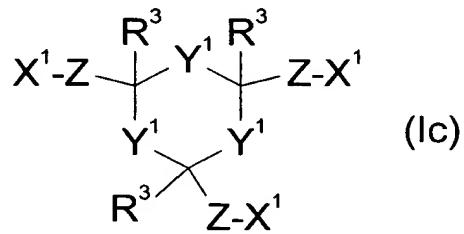
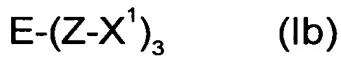
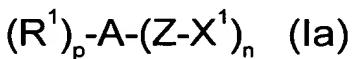
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MARKED UP CLAIMS (37 CFR §1.121)

IN THE CLAIMS:

Please amend claims 5, 7, 11-14, 33, 37, 39 and 45 as follows:

5. (Amended Twice) A liquid phase carrier (LPC) that has [formulae (I)] formula (Ia):



wherein: A is [carbon or] silicon; [E is nitrogen or P (O);] R¹ [and R³ are each independently] is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl or heterocyclylalkyl; p is 0 or 1; Z is any combination of 1-12 units selected from 1,2-, 1,3- or 1,4-phenylene and alkylene units, which units may be combined in any order [, with the proviso that if the LPC is of formula (Ia), then Z contains at least two phenylene or methylene units]; t is 1; X¹ is any reactive group which can be used in biopolymer synthesis; n is 3 or 4; [Y¹ is CH₂, NH, S or O; Y² is selected from CH or N;] R¹, [R³] X¹, [Y¹, Y²] and Z are unsubstituted or substituted with one or more substituents each independently selected from Q; and Q is halogen, hydroxy, nitrile, nitro, formyl, mercapto, carboxy, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxycarbonyl, aryloxycarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, perfluoroalkoxy, alkenyloxy, alkynyoxy, arylalkoxy, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylamino, dialkylamino, arylamino, diarylamino, alkylarylamino, alkylcarbonylamino, alkoxycarbonylamino, arylcarbonylamino, aryloxycarbonylamino, azido, alkylthio, arylthio, perfluoroalkylthio, thiocyanato, isothiocyanato, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl or diarylaminosulfonyl.

7. (Amended) The LPC of claim 5, wherein Z is a group with three or more points of attachment: one to A, [E, or the cyclic nucleus,] and the others to two or more X¹ groups.

11. (Amended) The LPC of claim [10] 5, wherein p is 0 and n is 4.

12. (Amended) The LPC of claim [11] 5, wherein Z is any combination of 1-12 units selected from 1,4-phenylene and methylene, which units may be combined in any order.

13. (Amended) The LPC of claim [11] 5, wherein Z is C₁₋₁₂ alkylene.

14. (Amended) The LPC of claim [11] 5, wherein X¹ is OH, SH or NH₂.

33. (Amended) A method of solution phase biopolymer synthesis, comprising the steps of:

(a) reacting an LPC of formula [Sp(X¹)_n] (R¹)_p-A-(Z_t-X¹)_n, with a first monomer N¹;

(b) separating and purifying the product of step (a) to afford a compound of formula [Sp(X¹)_n] (R¹)_p-A-(Z_t-X¹-N¹)_n;

(c) reacting the product of step (b) with a second monomer N², a dimer N²-N³ or a trimer N²-N³-N⁴; and

(d) repeating steps (b) and (c) to produce an LPC-bound biopolymer of formula [Sp(X¹-N¹-N²-...-N^m)_n] (R¹)_p-A-(Z_t-X¹-N¹-N²-...-N^m)_n, where m is 3 to 100, wherein:

[Sp is a polyvalent group that has more than two points of attachment, n corresponds to the number of points of attachment in Sp and]

A is silicon; R¹ is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl or heterocyclylalkyl; p is 0 or 1; Z is any combination of 0-12 units selected from 1,2-, 1,3- or 1,4-phenylene and alkylene, which units may be combined in any order; t is 0 or 1; X¹ is any reactive group which can be used in biopolymer synthesis; n is 3 or 4; R¹, X¹, and Z are unsubstituted or substituted with one or more substituents each independently selected from Q; and Q is halogen, hydroxy, nitrile, nitro, formyl, mercapto, carboxy, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxy carbonyl-

alkyl, aryloxycarbonyl, aryloxycarbonylalkyl, aminocarbonyl, alkylaminocarbonyl,
dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocar-
bonyl, alkoxy, aryloxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, arylalkoxy,
amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl,
diarylarninoalkyl, alkylamino, dialkylamino, arylamino, diarylamino,
alkylarylarnino, alkylcarbonylarnino, alkoxycarbonylarnino, arylcarbonylarnino,
aryloxycarbonylarnino, azido, alkylthio, arylthio, perfluoroalkylthio, thiocyanato,
isothiocyanato, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, aminosulfonyl,
alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl or diarylarnino-
sulfonyl; and

X¹ is a reactive group for biopolymer synthesis;

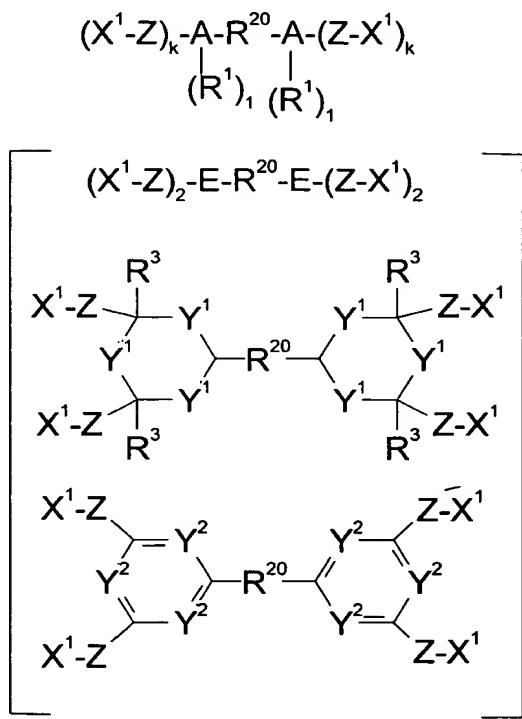
N¹, N², N³...N^m are biopolymer monomers; and

the dimers and trimers comprise the monomers.

37. (Amended) The method of claim 33, wherein n is [3-6] 3 or 4.

39. (Amended) The method of claim [38] 33, wherein X¹ is OH, SH, NH₂, COR⁵ or COOR⁴, where R⁴ is selected from hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl and heterocyclylalkyl; and R⁵ is halide, heteroaryl or pseudohalide.

45. (Amended) A liquid phase carrier (LPC) that has [formulae]
formula:



wherein: A is [carbon or] silicon; [E is nitrogen or P(O);] R¹ [and R³ are each independently] is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl or heterocyclylalkyl; Z is any combination of 1-12 units selected from 1,2-, 1,3- or 1,4-phenylene and alkylene, which units may be combined in any order [, with the proviso that if the LPC is of formula (Ia) or (Ib), then Z contains at least two phenylene or methylene units]; t is 0 or 1; X¹ is any reactive group which can be used in biopolymer synthesis; [Y¹ is CH₂, NH, S or O; Y² is selected from CH and N;] R¹, [R³,] X¹, [Y¹, Y²] and Z are unsubstituted or substituted with one or more substituents each independently selected from Q; and Q is halogen, hydroxy, nitrile, nitro, formyl, mercapto, carboxy, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl,

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MARKED UP CLAIMS C.F.R. 1.121

aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonyl-alkyl, aryloxycarbonyl, aryloxycarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, arylalkoxy, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylamino, dialkylamino, arylamino, diarylamino, alkylarylamino, alkylcarbonylamino, alkoxycarbonylamino, arylcarbonylamino, aryloxycarbonylamino, azido, alkylthio, arylthio, perfluoroalkylthio, thiocyanato, isothiocyanato, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl or diarylaminosulfonyl; R²⁰ is alkylene, alkenylene, alkynylene, arylene or heteroarylene; k is 2 or 3; and j is 0 or 1.